Executive Summary

Between 1979 and 1987, 151 pyrolytic carbon metacarpophalangeal (MCP) finger joint implants were implanted in 53 patients at the Mayo Clinic by Drs. Beckenbaugh and Linscheid. Of these, 147 implants were primary ball-and-cup uncemented pyrocarbon implants; 2 were condylar pyrocarbon implants (implants with a conical shaped bump in the center of the articulating surface of the distal component that interfaced with a groove on the proximal component's articulating surface); and 2 were revision ball-and-cup pyrocarbon implants (one uncemented and one cemented). The 53 patients who received 147 primary ball-and-cup uncemented pyrocarbon MCP finger joint implants represent the case series upon which the clinical data in this PMA is based.

In 1992, Ascension Orthopedics, Inc. was founded by Drs. Klawitter and Cook. Ascension Orthopedics, Inc. is the sponsor of this pre-market approval (PMA) application. The sponsor worked with Dr. Beckenbaugh to refine certain aspects of the prosthesis design, resulting in the Ascension® MCP device. The Ascension MCP device is not the version of the design that was used in the animal or clinical study but is the version of the design for which Ascension Orthopedics is requesting approval in their PMA. Similarities and differences between the pyrocarbon implant used in the animal and clinical studies and the Ascension MCP are presented in the Food and Drug Adminstration (FDA) pre-clinical review memo. The FDA pre-clinical review memo also includes a device description, identification of material properties, and a summary of animal testing, *in vitro* mechanical testing, finite element (FEA) stress and strain examinations, and material biocompatibility evaluations. The FDA pre-clinical review memo is provided in Tab 4 of the FDA Panel Pack.

Drs. Beckenbaugh and Linscheid did not consider themselves investigators or the Mayo Clinic an investigational site when they were implanting the pyrocarbon MCP finger joint devices. The sponsor stated that a prospective clinical investigation was not performed. Therefore, there was no prospective protocol or case report forms for the implantation of the 53 patients. The sponsor conducted a retrospective study by completely reviewing the medical records of each patient who received the MCP at Mayo Clinic.

Information provided in the Original PMA and Amendments 1 and 2 in support of the safety and effectiveness of the Ascension MCP was based on an independent report from a contract research organization (CRO), Boston Biostatistics, Inc. (BBI). BBI audited and validated the accuracy and completeness of the clinical records, extracted the information into computerized databases and analyzed the data. In addition, they performed an extensive review of the medical literature, established a literature control, and analyzed the Ascension MCP data compared to the control.

In the Original PMA, all information, clinical findings, and observations recorded in the source documents related to the patients' wrists, hands, fingers and MCP joints at baseline and at all follow-up visits were extracted and entered into the patient database. The patient database included demographic information (age, gender), diagnosis, hand dominance, general medical history, prior treatments, and all available follow-up data on objective clinical variables (MCP joint range of motion (flexion and extension), grip and pinch strength, and ulnar deviation) and subjective clinical attributes (pain, activity level, satisfaction, and cosmesis), radiographic information, surgical information, and all potential adverse events and complications. Kaplan-Meyer survival curves for the pyrocarbon MCP implants were provided, discussed, compared to the only survival curve found for MCP Swanson Silastic Devices in the literature (Hansraj, 1997), and a claim on non-inferiority was made. The demographic data, subjective attributes and objective variables at baseline and follow-up were analyzed and displayed in various tabular and graphical formats. For each subjective and objective endpoint, the sponsor presented descriptive statistics for the study population and a "subgroup" of the control articles and claimed "equivalence" without a formal statistical justification. Potential adverse events and complications related to device safety were identified and analyzed by diagnosis, operated and non-operated joint, finger, and hand.

Analysis of the Original PMA data by FDA resulted in major deficiencies regarding the following issues: (1) appropriateness of the literature controls; (2) failure to define a window of non-inferiority (i.e., delta) with regard to the Kaplan-Meyer survival analysis; (3) lack of a statistical comparison to the literature

control to support the non-inferiority claim for the Kaplan-Meyer survival analysis; and (4) lack of a statistical comparison to the literature control to support the claims of "equivalence" for the subjective and objective endpoints.

The sponsor responded to the major deficiencies identified by FDA in the Original PMA in Amendment 2. The sponsor computed 95% lower confidence bounds for the primary (implant survival) and "key" secondary effectiveness endpoints for the MCP study population to show that it is unlikely that study results could be inferior to the literature control data. The sponsor computed the probability that the MCP study results for the primary effectiveness endpoint (implant survival) were at least 10% below (delta = 10%) those of the literature control (Hansraj, 1997) at 10 years. This means that the 10-year survival for the study group could be up to 10 percentage points less than the control before it would be considered statistically inferior. This comparison is based, however, not on the observed rates, but the lower limit of the 95% confidence interval. The observed rate for 10-year survival was 84.3% for the pyrocarbon implant and 90.3% for the silastic spacer control (Hansraj, 1997). Assuming variance for the control, the p-value was calculated to be p=0.2032 rather than the traditional p=0.05. If one uses the more traditional p-value of p=0.05, the sponsor did not demonstrate that the pyrolytic carbon joint prosthesis was non-inferior to the Swanson Silastic joint spacer with respect to the primary effectiveness endpoint.

For many of the secondary endpoints, the average value for the literature controls was computed, a "clinically acceptable" delta was subtracted to define a lower threshold (a 25% absolute difference was selected for subjective measures like pain, patient satisfaction, and cosmesis and a 10° difference was selected for objective measures like extension lag, active flexion, arc of motion, and ulnar deviation), and the probability that the MCP study results could be below this threshold was computed. The results were broken down by 5-6 time intervals. There were many p-values that were less than p=0.05, and there were many that were greater than p=0.05. What stood out in the analysis was that the data were very sparse for the "key" secondary endpoints.

The sponsor's analysis in Amendment 2 raised the following issues, which were included in a letter from FDA to the sponsor on May 1, 2001 (the letter is included in Tab 9 of the FDA Panel Pack):

- FDA believed that the sponsor did not demonstrate that the pyrolytic carbon joint prosthesis was non-inferior to the Swanson Silastic joint prosthesis with respect to the primary effectiveness endpoint;
- FDA also believed that endpoints including pain, function (finger joint and hand), and radiographic data should be considered primary effectiveness endpoints in addition to implant survival;
- Also, rather than defining effectiveness in terms of individual patient and implant success and failure criteria incorporating the primary and secondary effectiveness endpoints, the sponsor compared the study and control means for each secondary endpoint separately. With each secondary endpoint presented and analyzed separately, the amount of information was very sparse. Therefore, FDA believed that the subsequent statistical analysis, presented in Amendment 2 and in which they compared the subject and control devices with respect to these secondary endpoints, may have contained patient selection bias;
- Also, rather than defining safety in terms of individual patient and implant success and failure criteria, the sponsor addressed safety only by descriptive statistics (i.e., proportions of each type of intra-operative and post-operative reportable event were compared between the study and control populations). In light of the fact that the patient follow-up rates were low, we believed there was little assurance that the safety data presented is representative of the entire patient population. Therefore, any subsequent statistical analysis in which a comparison is made between the subject and control devices with respect to intra-operative and post-operative reportable events may contain patient selection bias.

For the above reasons, FDA sent the sponsor the major deficiency letter dated May 1, 2001. However, we believed that the sponsor might have been able to provide well documented long-term case histories of each patient (considered to be valid scientific evidence, under 21 CFR 860.7) which might provide a more

complete picture of the safety and effectiveness of the Ascension MCP joint prosthesis than what was presented in the PMA up to that point. FDA advised the sponsor that by addressing items in our letter dated May 1, 2001, we were proposing one of potentially several ways in which they might present the clinical data to support the safety and effectiveness of the Ascension MCP joint prosthesis. The sponsor responded to the items listed in our letter dated May 1, 2001 with a reanalysis of the data. The sponsor's reanalysis is contained in Amendments 3 and 5.

The case series analysis provided in Amendments 3 and 5 was submitted in support of the safety and effectiveness of the Ascension MCP. With case series, the investigator does not control treatment assignment, endpoint ascertainment, selection biases, or confounding factors. Case series are typically used to generate hypotheses, not to test them. The information in Amendments 3 and 5 was not collected or analyzed by the CRO (BBI) but by Ascension Orthopedics, Inc.

In the sponsor's case series analysis of their data, presented in Amendments 3 and 5 of the PMA, the sponsor proposed that the patients be stratified and evaluated based on two baseline medical conditions: (1) osteoarthritis/post traumatic patients (OA/Trauma); and (2) rheumatoid arthritis/systemic lupus erythematosus patients (RA/SLE). Retrospective success/failure criteria with respect to device effectiveness endpoints (including criteria for implanted joint pain, joint function, and radiographic data) and success/failure criteria with respect to device safety endpoints (implant loosening, removal, dislocation, and post-operative implant fracture) were established. Separate success/failure criteria were defined for the OA/Trauma and RA/SLE patient groups (for the RA/SLE group, retrospective effectiveness criteria were defined for a 1-5 year treatment outcome analysis (in Amendment 3) and a longer-term treatment outcome analysis (in Amendment 5)). Each implant was determined to be either excellent, good, unsatisfactory, or indeterminate. Each implant with an excellent or good outcome was considered a success while an implant with an unsatisfactory outcome was considered a failure. Patients lacking information required as part of the definition of success and failure were termed to be indeterminate. Because the sponsor did not summarize the frequency and severity of all of the adverse events for the 53 case series patients in their analysis in Amendments 3 and 5, the sponsor's earlier summary in the Original PMA was used to evaluate overall device safety.

The frequency and severity of several key adverse events and the results of the sponsor's reanalysis, contained in Amendments 3 and 5 for the RA/SLE and OA/Trauma patient groups, are summarized in the Panel Questions in Tab 3 and in more detail in the clinical review memo in Tab 5 of the FDA Panel Pack.

A complete FDA analysis of the clinical data is provided in the FDA clinical review memo in Tab 5 of the FDA Panel Pack.

A complete FDA analysis of the statistical data is provided in the FDA statistical review memo in Tab 6 of the FDA Panel Pack.

The sponsor provided a summary of the clinical results in the Summary of Safety and Effectiveness Data, SSED, in Amendment 6 of the Sponsor's Panel Pack.